

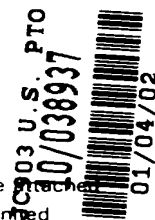
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: DAGGETT *et al.*  
Serial No.: 08/935,105  
Filed: September 29, 1997  
For: *HUMAN N-METHYL-D-  
ASPARTATE RECEPTOR  
SUBUNITS, NUCLEIC ACIDS  
ENCODING SAME AND USES  
THEREFOR*  
Art Unit: Unassigned  
Examiner: Unassigned

I hereby certify that this paper and the attached  
papers are being deposited with the United  
States Postal Service as first class mail in an  
envelope addressed to:  
Assistant Commissioner for Patents,  
Washington, D.C. 20231, on this date.

11/18/97  
Date

*Nancy V. McElrath*  
Nancy V. McElrath



INFORMATION DISCLOSURE STATEMENT  
IN ACCORDANCE WITH 37 C.F.R. § 1.97(b) and 1.98

Assistant Commissioner for Patents  
Washington, D.C. 20231

Dear Sir:

Because this Information Disclosure Statement is filed prior to receipt of a First Office Action on the Merits for the above-captioned application, a fee for filing this statement should not be due. If it is, however, determined that a fee is due, any fees that may be due in connection with filing this paper may be charged to Deposit Account No. 02-4070.

In accordance with the duty of disclosure imposed by 37 C.F.R. §1.56 to inform the Patent Office of all references known by Applicant or Applicant's representative that may be material to the examination of the subject application, Applicant's representative hereby provides this Information Disclosure Statement that is prepared in accordance with 37 C.F.R. §§1.97-1.98. Forms PTO-1449 (10 pages) are provided herewith. Copies of the references listed on the Form PTO-1449 are not provided herewith as they have been previously provided in connection with U.S. Serial No. 08/231,193, which is relied upon for an earlier filing date in accordance with 35 U.S.C. §120.

**U.S.S.N. 08/935,105**  
**DAGGETT *et al.***  
**INFORMATION DISCLOSURE STATEMENT**

The document CK that is newly cited in connection with this application is attached hereto and is in the English language. Other than as noted below, the documents listed on the Forms PTO-1449 are in the English language. The Japanese patent no. 6014783 (item O) is in the Japanese language. The foreign patents PCT International Patent Nos. 93/23536, 93/25679, 94/01094, 94/04698, and 95/26401 (items T, V, W, A, and AA respectively) have English language abstracts. Hence, in accordance with the requirements of 37 C.F.R. §1.98, as amended effective March 16, 1992, no further explanation of the listed items are necessary.

The Examiner's attention is directed to reference BI (Hess *et al.*) which is an abstract that published in connection with the 1994 Biophysical Society Annual Meeting. The abstract reports isolation of cDNA clones encoding human N-methyl-D-aspartate receptor subunits, but does not provide the nucleotide sequences of the human clones. A poster presented at the poster session showed a protein sequence comparison among the deduced receptor proteins hNMDAR1A, hNMDAR2A, and hNMDAR2B, but did not provide any nucleotide sequences of the corresponding clones. A copy of the poster is provided in reference BI.

Although these documents are made known to the Patent and Trademark Office in compliance with Applicant's duty of disclosure, such disclosure is not to be construed as an admission by Applicant or Applicant's representative that any of the references, singly or in any combination thereof, is effective as prior art against the subject application. In accordance with 37 C.F.R. §1.97(h), the filing of this Information Disclosure Statement shall not be construed to mean that a search has been made or that no other material information as defined in 37 C.F.R. §1.56(b) exists.

**U.S.S.N. 08/935,105**  
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Applicant also makes known to the Examiner the following related, co-pending applications:

<u>U.S.S.N</u>	<u>Inventor</u>	<u>Filing date</u>
08/052,449	Daggett <i>et al.</i>	4/20/93
08/480,474	Daggett <i>et al.</i>	6/6/95
08/486,273	Daggett <i>et al.</i>	6/6/95
08/940,086	Daggett <i>et al.</i>	9/29/97
08/940,035	Daggett <i>et al.</i>	9/29/97

Corresponding International Applications


WO94/24284	4/20/94
G.B. 1503689.3	4/20/94
EP 94916547.6-1212 (PUB. NO. 0696320)	4/20/94
AU 68175/94	4/20/94
JP 523578/94	4/20/94
CA 2159106	4/20/94

Applicant respectfully requests that the Examiner review the foregoing reference and make it of record in the file history of the above-captioned application.

\* \* \*

Respectfully submitted,  
BROWN, MARTIN, HALLER & McCLAIN

By:

  
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Registration No. 33,779

Attorney Docket No. 6362-9383D  
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LIST OF PATENTS AND PUBLICATIONS FOR  
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JC903 U.S. PTO  
10/038937  
01/04/02

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER							DATE	NAME	CLASS	SUB CLASS	FILING DATE
	A	4	8	3	7	1	4	8	6/6/89	Cregg	435	172.3	10/30/84
	B	4	8	5	5	2	3	1	8/8/89	Stroman <i>et al.</i>	435	68	9/25/85
	C	4	8	8	2	2	7	9	11/21/89	Cregg	435	68	10/25/85
	D	4	9	2	9	5	5	5	5/29/90	Cregg <i>et al.</i>	435	172.3	10/19/87
	E	5	0	2	4	9	3	9	6/18/91	Gorman	435	69.1	9/25/87
	F	5	0	2	8	7	0	7	7/2/91	Nichols <i>et al.</i>	546	156	11/20/89
	G	5	2	0	2	2	5	7	4/13/93	Heinemann <i>et al.</i>	435	252.3	6/21/91
	H	5	4	0	1	6	2	9	3/28/95	Harpold <i>et al.</i>	435	6	8/7/90
	I	5	4	0	3	4	8	4	4/4/95	Ladner <i>et al.</i>	435	235.1	1/26/93
	J	5	4	3	6	1	2	8	7/25/95	Harpold <i>et al.</i>	435	6	1/27/93

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER							DATE	COUNTRY	CLASS	SUB CLASS	Translation NO YES	
	K	0	6	0	0	2	7	8	6/8/94	EP A2	--	--		
	L	0	6	0	6	7	3	4	7/20/94	EP	--	--		
	M	0	6	7	4	0	0	3	9/27/95	EP	--	--		
	N	2	2	9	1	6	4	7	1/31/96	GB	--	--		
	O	6	0	1	4	7	8	3	1/25/94	JP	--	--		
	P	9	1	0	6	6	4	8	5/16/91	PCT	--	--		
	Q	9	2	2	3	7	6	9	11/12/92	GB	--	--		
	R	9	3	0	7	0	2	6	4/2/93	GB	--	--		
	S	9	3	1	3	4	2	3	7/8/93	PCT	--	--		
	T	9	3	2	3	5	3	6	11/25/93	PCT	--	--		
	U	9	3	2	4	6	2	9	12/9/93	PCT	--	--		

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		DOCUMENT NUMBER							DATE	COUNTRY	CLASS	SUB CLASS	Translation NO YES	
	V	9	3	2	5	6	7	9	12/23/93	PCT	--	--	*	
	W	9	4	0	1	0	9	4	1/20/94	PCT	--	--	*	
	X	9	4	0	4	6	9	8	3/3/94	PCT	--	--	*	
	Y	9	4	0	6	4	2	8	3/31/94	PCT	--	--		
	Z	9	4	1	1	5	0	1	5/26/94	PCT	--	--		
	AA	9	5	2	6	4	0	1	10/5/95	PCT	--	--	*	

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AB	Abbott, NMDA receptor cloned, <i>Trends Pharmacol. Sci.</i> 12:449 (1991)
AC	Abbott, NMDA receptor subunit cloned, <i>Trends Pharmacol. Sci.</i> 12:334 (1991)
AD	Abe <i>et al.</i> , Molecular characterization of a novel metabotropic glutamate receptor mGluR5 coupled to inositol phosphate/Ca <sup>2+</sup> signal transduction, <i>J. Biol. Chem.</i> 267:13361-13368 (1992)
AE	Albin <i>et al.</i> , Abnormalities of striatal projection neurons and <i>N</i> -methyl-D-aspartate receptors in presymptomatic Huntington's Disease, <i>N. Engl. J. Med.</i> 322(18):1293-1298 (1990)
AF	Anantharam <i>et al.</i> , Combinatorial RNA splicing alters the surface charge on the NMDA receptor, <i>FEBS Lett.</i> 305(1):27-30 (1992)
AG	Bahouth <i>et al.</i> , Immunological approaches for probing receptor structure and function, <i>Trends Pharmacol. Sci.</i> 12:338-343 (1991)
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AI	Beal, Mechanisms of excitotoxicity in neurologic diseases, <i>FASEB J.</i> 6:3338-3344 (1992)
AJ	Ben-Ari <i>et al.</i> , Protein kinase C modulation of NMDA currents: an important link for LTP induction, <i>Trends Neurosci.</i> 15:333-339 (1992)
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AM	Bradford, A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding, <i>Anal. Biochem.</i> 72:248 (1976)
AN	Bristow <i>et al.</i> , The glycine/NMDA receptor antagonist R-(+)-HA-966, blocks activation of the mesolimbic dopaminergic system induced by phencyclidine and dizcilpine (MK-801) in rodents, <i>Br. J. Pharmacol.</i> 108:1156-1163 (1993)
AO	Choi, Calcium-mediated neurotoxicity: Relationship to specific channel types and role in ischemic damage, <i>Trends Neurosci.</i> 11(10):465-469 (1988)
AP	Choi, Glutamate neurotoxicity and diseases of the nervous system, <i>Neuron</i> 1:623-634 (1988)
AQ	Ciba-Geigy Unveils Research Agreement with SIBIA of U.S., <i>The Wall Street Journal</i> (September 17, 1992)
AR	Coyle <i>et al.</i> , Oxidative stress, glutamate, and neurodegenerative disorders, <i>Science</i> 262:689-695 (1993)
AS	Daggett <i>et al.</i> , Cloning and functional characterization of three splice variants of the human NMDAR1 receptor, <i>Biophys J.</i> , 36(2):447 (1994)
AT	Dascal, The use of <i>Xenopus</i> oocytes for the study of ion channels, <i>CRC Critical Reviews in Biochemistry</i> 22(4):317-387 (1987)
AU	Donnelly and Pallotta, Single-channel currents from diethylpyrocarbonate-modified NMDA receptors in cultured rat brain cortical neurons, <i>J. Gen. Physiol.</i> 105:837-859 (1995)
AV	Durand <i>et al.</i> , Cloning of an apparent splice variant of the rat <i>N</i> -methyl-D-aspartate receptor NMDAR1 with altered sensitivity to polyamines and activators of protein kinase C, <i>Proc. Natl. Acad. Sci. USA</i> 89:9359-9363 (1992)
AW	Egebjerg <i>et al.</i> , Intron sequence directs RNA editing of the glutamate receptor subunit GluR2 coding sequence, <i>Proc. Natl. Acad. Sci. USA</i> 91:10270-10274 (1994)
AX	Felder <i>et al.</i> , A transfected m1 muscarinic acetylcholine receptor stimulates adenylate cyclase via phosphatidylinositol hydrolysis, <i>J. Biol. Chem.</i> 264:20356-20362 (1989)
AY	Fisher and Aronson, Characterization of the cDNA and genomic sequence of a G protein $\gamma$ subunit ( $\gamma_5$ ), <i>Mol. Cell. Bio.</i> 12:1585 (1992)
AZ	Foldes <i>et al.</i> , Cloning and sequence analysis of cDNAs encoding human hippocampus <i>N</i> -methyl-D-aspartate receptor subunits: Evidence for alternative splicing, <i>Gene</i> 131:293-298 (1993)

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	BC	Gereau and Conn, Multiple presynaptic metabotropic glutamate receptors modulate excitatory and inhibitory synaptic transmission in hippocampal area CA1, <i>J. Neurosci</i> 15(10):6879-6889 (1995)
	BD	Greenamyre <i>et al.</i> , Synaptic localization of striatal NMDA, quisqualate and kainate receptors, <i>Neurosci. Lett.</i> 101:133-137 (1989)
	BE	Grimwood <i>et al.</i> , Interactions between the glutamate and glycine recognition sites of the <i>N</i> -methyl-D-aspartate receptor from rat brain, as revealed from radioligand binding studies, <i>J. Neurochem.</i> 60:1729-1738 (1993)
	BF	Gubler <i>et al.</i> , A simple and very efficient method for generating cDNA libraries, <i>Gene</i> 25:263-269 (1983)
	BG	Gunasekar <i>et al.</i> , NMDA receptor activation produces concurrent generation of nitric oxide and reactive oxygen species: Implication for cell death, <i>J. Neurochem.</i> 65:2016-2021 (1995)
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	BJ	Hess <i>et al.</i> , Biophysical properties of human NMDA receptors stably expressed in mammalian cells, <i>Soc. Neurosci. Abstr.</i> 21:1-3 (1995)
	BK	Hoffman, NMDA receptor cloned — twice! <i>Science</i> 254:801-802 (1991)
	BL	Hollman <i>et al.</i> , Zinc potentiates agonist-induced currents at certain splice variants of the NMDA receptor, <i>Neuron</i> 10:943-954 (1993)
	BM	Hollman <i>et al.</i> , Cloned glutamate receptors, <i>Annu. Rev. Neurosci.</i> 17:31-108 (1994)
	BN	Hurley <i>et al.</i> , Isolation and characterization of a cDNA clone for the $\gamma$ subunit of bovine retinal transducin, <i>Proc. Natl. Acad. Sci. USA</i> 81:6948 (1984)
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BQ	Jones <i>et al.</i> , Characterization of the binding of radioligands to the <i>N</i> -methyl-D-aspartate, phencyclidine, and glycine receptors in buffy coat membranes, <i>J. Pharmacol. Meth.</i> 21:161 (1989)
BR	Kantak <i>et al.</i> , Effects of <i>N</i> -methyl-D-aspartate antagonists in rats discriminating different doses of cocaine: Comparisons with direct and indirect dopamine agonists, <i>J. Pharmacol. Exper. Therap.</i> 274:657-665 (1995)
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BU	Kishimoto <i>et al.</i> Studies on the phosphorylation of myelin basic protein by protein kinase C and adenosine 3':5'-monophosphate-dependent protein kinase, <i>J. Biol. Chem.</i> 260:12492-12499 (1985)
BV	Kisselev <i>et al.</i> , Receptor-G protein coupling is established by a conformational switch in the $\beta\gamma$ complex, <i>Proc. Natl. Acad. Sci. USA</i> 92:9102-9106 (1995)
BW	Kleuss <i>et al.</i> , Selectivity in signal transduction determined by $\gamma$ subunits of heterotrimeric G proteins, <i>Science</i> 259:832 (1993)
BX	Köhr <i>et al.</i> , NMDA receptor Channels: Subunit-specific potentiation by reducing agents, <i>Neuron</i> 12:1031-1040 (1994)
BY	Kozak, Structural features in eukaryotic mRNAs that modulate the initiation of translation, <i>J. Biol. Chem.</i> 266:19867-19870 (1991)
BZ	Krieg and Melton, Functional messenger RNAs are produced by SP6 <i>in vitro</i> transcription of cloned cDNAs, <i>Nucleic Acids Research</i> 12:7057-7070 (1984)
CA	Kumar <i>et al.</i> , Cloning of cDNA for the glutamate-binding subunit of an NMDA receptor complex, <i>Nature</i> 354:70-73 (1991)
CB	Kutsuwada <i>et al.</i> , Molecular diversity of the NMDA receptor channel, <i>Nature</i> 358:36-41 (1992)
CC	Kyte and Doolittle, A simple method for displaying the hydropathic character of a protein, <i>J. Mol. Biol.</i> 157:105 (1982)
CD	Landwehrmeyer <i>et al.</i> , NMDA receptor subunit mRNA expression by projection neurons and interneurons in rat striatum, <i>J. Neurosci.</i> 15(7): 5297-5307 (1995)

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CF	Linder and Gilman, G proteins, <i>Scientific American</i> 267:56-65 (1992)
CG	Liu <i>et al.</i> , Mutational analysis of the relative orientation of transmembrane helices I and VII in G protein-coupled receptors, <i>J. Biol. Chem.</i> 270(3):19532-19539 (1995)
CH	Lynch <i>et al.</i> , Pharmacological characterization of heterodimeric NMDA receptors of NR1a and 2B subunits: Differences with receptors formed from NR 1a and 2A, <i>J. Neurochem.</i> 64:1462-1468 (1995)
CI	Masayuki, Human mRNA for key subunit of the N-methyl-D-aspartate receptor, DDBJ database (7/20/93)
CJ	Masu <i>et al.</i> , Sequence and expression of a metabotropic glutamate receptor, <i>Nature</i> 349:760-765 (1991)
CK	Matsui <i>et al.</i> , Functional comparison of D-serine and glycine in rodents: the effect on cloned NMDA receptors and the extracellular concentration, <i>J. Neurochemistry</i> 65:454-458 (1995)
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CM	Meguro <i>et al.</i> , Functional characterization of a heteromeric NMDA receptor channel expressed from cloned cDNAs, <i>Nature</i> 357:70-74 (1992)
CN	Meldrum, Possible therapeutic applications of antagonists of excitatory amino acid neurotransmitters, <i>Clin. Sci.</i> 68:113-122 (1985)
CO	Meldrum <i>et al.</i> , Excitatory amino acid neurotoxicity and neurodegenerative disease, <i>Trends Pharmacol. Sci.</i> 11:379-387 (1990)
CP	Minakami <i>et al.</i> , The expression of two splice variants of metabotropic glutamate receptor subtype 5 in the rat brain and neuronal cells during development, <i>J. Neurochem.</i> 65:1536-1542 (1995)
CQ	Monaghan <i>et al.</i> , The excitory amino acid receptors: Their classes, pharmacology, and distinct properties in the function of the central nervous system, <i>Ann. Rev. Pharmacol. Toxicol.</i> 29:365-402 (1980)
CR	Monyer <i>et al.</i> , Heteromeric NMDA receptors: Molecular and functional distinction of subtypes, <i>Science</i> 256:1217-1221 (1992)
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CT	Moriyoshi <i>et al.</i> , Molecular cloning and characterization of the rat NMDA receptor, <i>Nature</i> 354:31-37 (1991)
CU	Nakajima <i>et al.</i> , Direct linkage of three tachykinin receptors to stimulation of both phosphatidylinositol hydrolysis and cyclic AMP cascades in transfected Chinese hamster ovary cells, <i>J. Biol. Chem.</i> 267:2437-2442 (1992)
CV	Nakanishi, Molecular diversity of glutamate receptors and implications for brain function, <i>Science</i> 258:597-602 (1992)
CW	Nicoletti <i>et al.</i> , The activation of inositol phospholipid metabolism as a signal-transducing system for excitory amino acids in primary cultures of cerebellar granule cells, <i>J. Neurosci.</i> 6:1905 (1986)
CX	SIBIA/Ciba-Geigy agreement, <i>UCSD Connect</i> (September 16, 1992)
CY	Ogita <i>et al.</i> , A possible role of glutathione as an endogenous agonist at the <i>N</i> -methyl-D-aspartate recognition domain in rat brain, <i>J. Neurochem.</i> 64:1088-1096 (1995)
CZ	Other News to Note, <i>BioWorld Today</i> , 6 (April 15, 1994)
DA	O'Connor <i>et al.</i> , Tetanically induced LTP involves a similar increase in the AMPA and NMDA receptor components of the excitory postsynaptic current: Investigations of the involvement of mGlu receptors, <i>J. Neurosci.</i> 15(3):2013-2020 (1995)
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DB	Pin <i>et al.</i> , Alternative splicing generates metabotropic glutamate receptors inducing different patterns of calcium release in <i>Xenopus</i> oocytes, <i>Neurobiology</i> 89:10331-10335 (1992)
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DD	Potter, Sibia to collaborate with Ciba-Geigy, <i>BioWorld Today</i> 3:1 (Sep. 17, 1992)
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FORM PTO-1449 (Modified)	ATTY. DOCKET NO. 6362-9383D	SERIAL NO. 08'935,105
	APPLICANT DAGGETT <i>et al.</i>	
	FILING DATE September 29, 1997	GROUP Unassigned

LIST OF PATENTS AND PUBLICATIONS FOR  
APPLICANT'S INFORMATION DISCLOSURE  
STATEMENT

OTHER ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	DH	Sambrook <i>et al.</i> , <i>Molecular Cloning. A Laboratory Manual</i> , 2d Ed., Cold Spring Harbor Laboratory Press (1989)
	DI	Sanes <i>et al.</i> , Use of a recombinant retrovirus to study post-implantation cell lineage in mouse embryos, <i>EMBO J.</i> 5(12):3133-3142 (1986)
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	DU	Stillman <i>et al.</i> , Replication and supercoiling of simian virus 40DNA in cell extracts from human cells, <i>Mol. Cell. Biol.</i> 5:2051-2060 (1985)
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## OTHER ART (Including Author, Title, Date, Pertinent Pages, Etc.)

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DZ	Sullivan <i>et al.</i> , Identification of two cysteine residues that are required for redox modulation of the NMDA subtype of glutamate receptor, <i>Neuron</i> 13:929-936 (1994)
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EB	Tamir <i>et al.</i> , G-protein $\beta\gamma$ forms: Identity of $\beta$ and diversity of $\gamma$ subunits, <i>Biochemistry</i> 30:3929 (1991)
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EF	Urlaub <i>et al.</i> , Effect of gamma rays at the dihydrofolate reductase locus: Deletions and Inversions, <i>Somatic Cell and Mol. Genetics</i> 12(6):555-566 (1986)
EG	Varney <i>et al.</i> , Stable expression and characterization of recombinant human dimeric NMDA receptor subtypes 1A/2A and 1A/2B in mammalian cells, <i>Soc. Neurosci. Abstr.</i> (1995)
EH	Vornov <i>et al.</i> , Enhancement of NMDA receptor-mediated neurotoxicity in the hippocampal slice by depolarization and ischemia, <i>Brain Res.</i> 555:99-106 (1991)
EI	Waechter and Baserga, Effect of methylation on expression of microinjected genes, <i>Proc. Natl. Acad. Sci. USA</i> 79:1106-1110 (1982)
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EK	Wahlestedt <i>et al.</i> , Antisense oligodeoxynucleotides to NMDA-R1 receptor channel protect cortical neurons from excitotoxicity and reduce focal ischaemic infarctions, <i>Nature</i> 363:260-263 (1993)
EL	Wenzel <i>et al.</i> , Distribution of NMDA receptor subunit proteins NR2A, 2B, 2C, and 2D in rat brain, <i>NeuroReport</i> 7:45-48 (1995)
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